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5-Benzothiazole substituted pyrimidine derivatives as HCV replication (replicase) inhibitors

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ABSTRACT

Based on a previously identified HCV replication (replicase) inhibitor **1**, SAR efforts were conducted around the pyrimidine core to improve the potency and pharmacokinetic profile of the inhibitors. A benzothiazole moiety was found to be the optimal substituent at the pyrimidine 5-position. Due to potential reactivity concern, the 4-chloro residue was replaced by a methyl group with some loss in potency and enhanced rat in vivo profile. Extensive investigations at the C-2 position resulted in identification of compound **16** that demonstrated very good replicon potency, selectivity and rodent plasma/target organ concentration. Inhibitor **16** also demonstrated good plasma levels and oral bioavailability in dogs, while monkey exposure was rather low. Chemistry optimization towards a practical route to install the benzothiazole moiety resulted in an efficient direct C–H arylation protocol.

1. Introduction

An estimated 3% of the human population is infected with hepatitis C virus (HCV).[1] It is a global health burden and the leading cause of liver cirrhosis, hepatocellular carcinoma and liver failure in humans. HCV is a positive stranded RNA virus belonging to the *Flaviviridae* family. Pegylated α-interferon and ribavirin combination therapy, the standard-of-care (SOC) until recently, does not target the virus specifically.[2] It is effective in less than 50% of genotype 1 patients, a population more prevalent in North America, Europe and Japan. Furthermore, the undesirable side effects associated with the SOC makes it less than ideal for patient compliance.[3] The past decade saw an explosion of growth towards discovering novel small molecule direct-acting antivirals (DAA) that inhibit HCV replication. These efforts resulted in the recent regulatory approval of NS3 protease inhibitors, boceprevir and telaprevir that improved the cure rates when added to the SOC.[4] Several other DAAs (NS3 protease inhibitors, NS5B nucleoside and non-nucleoside inhibitors, and NS5A inhibitors) are in various stages of clinical trials.[5] Due to the high mutation rate and genetic variability of HCV (at least six genotypes, with numerous subtypes), novel small molecules with distinct resistance profile that will likely become part of a combination regimen are highly sought-after.

Our previous efforts[6] towards identification of novel small molecule inhibitors of hepatitis C virus replication resulted in carbanucleoside-like compound **1** with modest potency in the HCV genotype 1b subgenomic replicon assay,[7] and low rat plasma exposure. Earlier target engagement studies suggested that compounds of type **1** could possibly inhibit the HCV replication complex (replicase). SAR studies around the aforementioned core demonstrated the importance of an aryl substituted alkynyl linkage at the 5-position of the pyrimidine ring. In an attempt to probe additional tolerated functionality at the pyrimidine 5-position that could also improve the potency/pharmacokinetic profile of the inhibitors, we replaced the 5-alkynyl linkage with an aryl moiety. Herein we describe our investigations toward structures of type **2** (Fig. 1) that resulted in several compounds with improved replicon potency.

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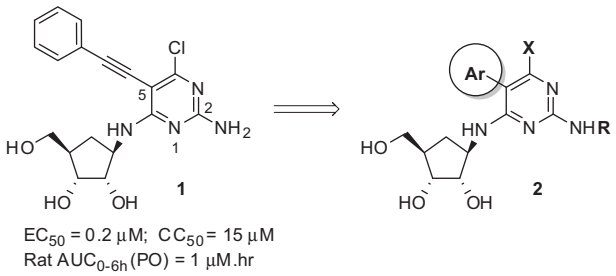


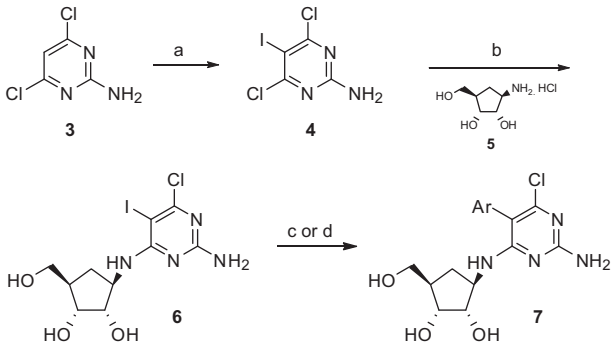
Figure 1. Design of inhibitors based on lead **1**.

Further in vivo evaluations provided compounds with enhanced rat plasma exposure and high levels of target organ coverage.

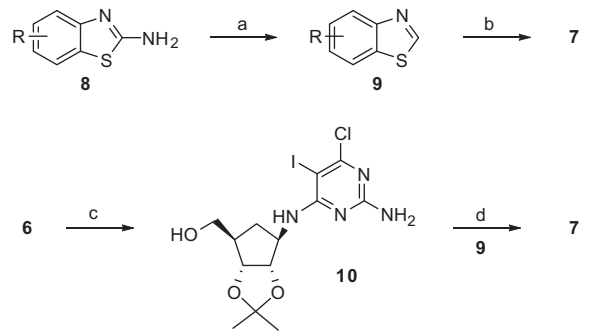
Synthetic chemistry routes for the preparation of 5-aryl target compounds are described in Schemes 1–4. Iodination of commercially available 2-amino-4,6-dichloro pyrimidine **3** resulted in **4**. Treatment of **4** with carbasugar **5** provided the key intermediate **6** in good yield. A variety of aryl groups were installed at the 5-position of the pyrimidine ring via Suzuki or Stille reaction of iodide **6** with readily available aryl boronic acids or aryl tri-*n*-butyl stannanes, respectively.[8] It was found that the required targets **7** could be obtained in adequate yield using microwave conditions as shown in Scheme 1.

Target compounds **21**–**32** (Table 1) containing unsubstituted aromatic group at the 5-position of the pyrimidine moiety were prepared using the route shown in Scheme 1. Installation of the substituted benzothiazole moiety at the 5-position of the pyrimidine ring was accomplished using the synthetic sequence shown in Scheme 2. The substituted benzothiazole precursors **9** were obtained from the corresponding 2-amino benzothiazole compounds **8** via diazotization chemistry. Lithiation of **9** followed by quenching with tri-*n*-butylstannyl chloride provided 2-stannyl benzothiazoles that subsequently underwent the previously described Stille protocol with iodide **6** to afford some of the required targets **7**. Alternatively, certain targets of type **7** were obtained via direct C–H arylation of benzothiazoles **9** with diol-protected iodide **10**. It was found that both palladium and copper catalysts were required for the direct arylation reaction.[9] Diol protection, as the corresponding acetonide, was also crucial for the success of the reaction. It is worth noting that the direct arylation reaction proceeded successfully with a fully functionalized pyrimidine motif under microwave conditions, albeit in low yield.

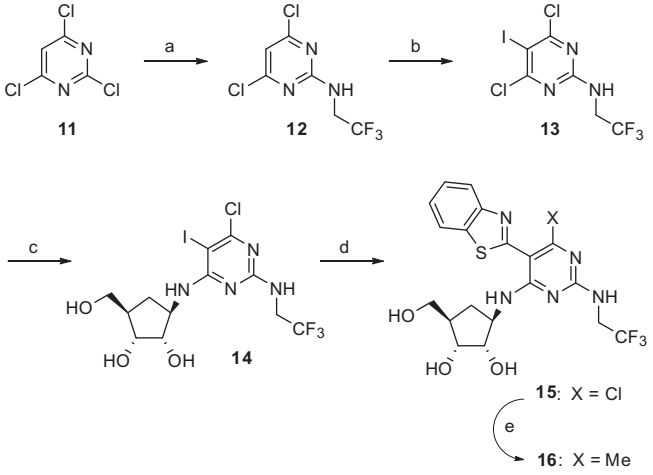
Scheme 3 depicts the representative synthesis of some of the inhibitors with C-2 and C-4 modified pyrimidine core. Treatment



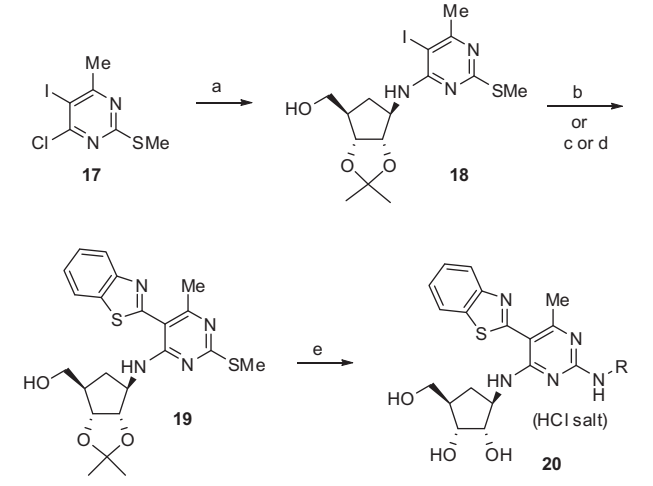
Scheme 1. Reagents and conditions. (a) ICl, gl. AcOH, 5 h (79%); (b) **5**, EtOH, Et_3N, reflux, 16 h (80%); (c) $ArB(OH)_2$, $PdCl_2(dppf)_2$, K_2CO_3, DME/water, microwave 120 °C, 5–15 min (20–42%); (d) nBu_3SnAr, $PdCl_2(Ph_3P)_2$, CuI, Et_3N, DMF, microwave 120 °C, 15 min (29–50%).



Scheme 2. Reagents and conditions. (a) *t*-amylnitrite, THF, reflux, 30 min; (b) (i) *n*BuLi, nBu_3SnCl, THF, −78 °C, 3 h (used as crude); (ii) **6**, $PdCl_2(Ph_3P)_2$, CuI, Et_3N, DMF, microwave 120 °C, 15 min (<20%); (c) 2,2-dimethoxypropane, MsOH, acetone, 0–25 °C, 16 h (quant.); (d) (i) **9**, $Pd(Ph_3P)_4$, CuI, Cs_2CO_3, DMF, microwave 120 °C, 15 min (5–13%); (ii) Aq. 1 N HCl, MeOH, 25 °C, 12 h (quant.).

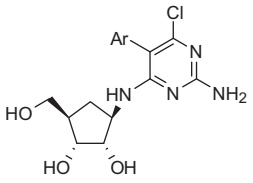


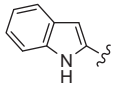
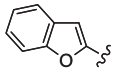
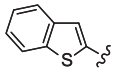
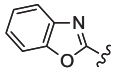
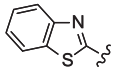
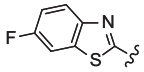
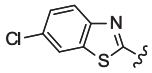
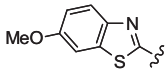
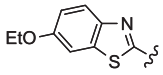
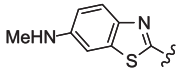
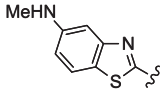
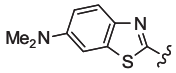
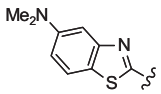
Scheme 3. Reagents and conditions. (a) $CF_3CH_2NH_2$, Et_3N, THF (16%); (b) ICl, gl. AcOH (quant.); (c) **5**, EtOH, Et_3N, reflux, 16 h (87%); (d) tri-*n*-butylstannyl benzothiazole, $Pd(Ph_3P)_4$, CuI, Et_3N, dioxane, 100 °C, ~1 h (57%); (e) $MeB(OH)_2$, $PdCl_2(Ph_3P)_2$, K_2CO_3, dioxane/water, 100 °C, 2 h (43%).



Scheme 4. Reagents and conditions. (a) (i) **5**, EtOH, Et_3N, reflux, 16 h; (ii) 2,2-dimethoxypropane, MsOH, acetone, 0–25 °C (79% for two steps); (b) tri-*n*-butylstannyl benzothiazole, $Pd(Ph_3P)_4$, CuI, Et_3N, dioxane, 100 °C, 16 h (80%); (c) benzothiazole, $Pd(Ph_3P)_4$, CuI, Cs_2CO_3, DMF, 100 °C, 2 h (45%); (d) benzothiazole, $Pd(dppf)_2Cl_2$, Ag_2CO_3, Ph_3P, MeCN, 75 °C, 24 h (70%); (e) (i) mCPBA, CH_2Cl_2, 0–25 °C; (ii) RNH_2, MeCN, 80–100 °C, 12–16 h; (iii) Aq. HCl, dioxane, MeOH (60–80% for three steps).

Table 1
Evaluation of 5-aryl series



Compd #	Ar	EC_{50} (μM)	MTS/GAPDH CC_{50} (μM)
21		>25	>25/–
22		>25	>25/>25
23		>25	>25/—
24		4	>25/>25
25		>25	—/>25
26		>25	>25/>25
27		3	>25/>25
28		7	25/—
29		0.3	>25/—
30		>25	—/>25
31		0.05	15/12
32		0.02	18/14
33		0.18	>25/>25
34		0.65	>25/16
35		0.045	>25/>25
36		0.03	25/>25
37		0.05	16/6
38		0.02	14/20
39		1	>25/>25
40		0.035	21/25

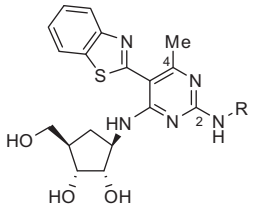
of trichloropyrimidine **11** with a suitable amine, trifluoroethyl amine, provided 2-amino substituted pyrimidine **12**.[10] A substantial amount (~50–60%) of the 4-regioisomeric byproduct (structure not shown) was easily separated by silica chromatography. Iodination and subsequent reaction with carbasugar **5** followed earlier described conditions to afford intermediate **14**. Stille reaction of **14** with tri-*n*-butylstannyl benzothiazole using palladium and copper catalysts provided **15** in moderate yields. The methyl group at the 4-position was installed via Suzuki reaction with methyl boronic acid to provide the required target compound **16**.

While the synthetic sequence shown in Scheme 3 was suitable for the initial series target compounds, it was not practical for SAR development. Since our intention was to probe the requirement for pyrimidine C-2 substitution, a more robust route that was amenable for late stage C-2 amino installation was necessary. Such a route is shown in Scheme 4. Thus, carbasugar **5** was treated with known 2-methylthio pyrimidine derivative **17**,[11] followed by diol protection to give the 5-iodo intermediate **18**. Employing the Stille protocol described above, **18** was smoothly converted to the key 5-benzothiazole intermediate **19**. At this juncture, due to several reasons ((a) limited availability of stannyl reagent from commercial sources, and (b) requirement of large quantities of environmentally unfriendly stannyl reagent for multigram quantities of **19**), we explored other methods of 5-benzothiazole installation. We were pleased to find that the direct C–H arylation of benzothiazole using conditions described earlier worked well to provide **19** in moderate yield. Further investigations resulted in an optimized C–H arylation protocol that employed palladium catalyst, triphenyl phosphine and silver carbonate, and provided the key intermediate **19** in 70% isolated yield. Intermediate **19** was then processed in three steps to targets of type **20** as shown in Scheme 4.

Previously we had identified compound **1** as a HCV replication (replicase) inhibitor with modest replicon potency, and low rat plasma exposure. Our earlier work revealed an alkenyl, or more importantly, an alkynyl moiety as the preferred substituent at the 5-position of the pyrimidine ring. As a logical way forward in developing the SAR around structure **1**, and possibly to improve the potency/pharmacokinetic profile of the inhibitors, we designed targets of type **2** with an aryl ring as the pyrimidine 5-substituent. These designed compounds were synthesized as shown in Schemes 1 and 2, and the potency data are shown in Table 1. The initial set of targets prepared, monocyclic aryl rings at the pyrimidine 5-position (**21**–**27**), were largely inactive. Only the furanyl (**24**) and thiazolyl (**27**) substituent showed marginal levels of replicon potency, albeit less potent compared to **1**. Interestingly, the benzofuranyl compound **29** restored the replicon potency while improving the selectivity index (EC_{50}/CC_{50}), compared to **1**. Installation of benzoxazolyl (**31**) or benzothiazolyl (**32**) moiety onto the pyrimidine motif had a profound impact on potency, with replicon EC_{50} equal to 0.05 or 0.02 μM, respectively. Replicon data for compounds **28** and **30** indicated that only limited aryl substituents were tolerated at the 5-position of pyrimidine ring. Having established the optimum group at 5-position, we then probed the effect of introducing additional functionality on the benzothiazolyl moiety. While halo substituents (**33** and **34**) resulted in potency loss, alkoxy groups (**35** and **36**) retained potency while improving the selectivity. Introduction of a methylamino group at the 5- or 6-position on the benzothiazolyl ring (**37** and **38**) provided equipotent inhibitors. However, a dimethylamino functionality was accommodated only at the 5-position (**40**) and not at the 6-position (**39**) of the benzothiazolyl moiety.

Since a naked benzothiazolyl moiety at the 5-position of the pyrimidine ring provided a potent inhibitor with acceptable selectivity, we decided to carry out C-2 modifications on substrate of type **32** (Table 2). Before we embarked on such an investigation, we were concerned with the possible reactivity of 4-chloro group

Table 2
Evaluation of C-2 amino substituent.



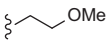
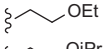
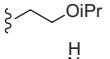
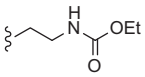
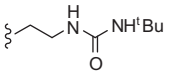
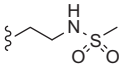
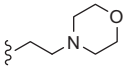
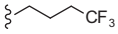
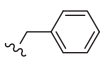
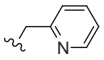
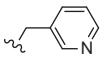
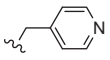
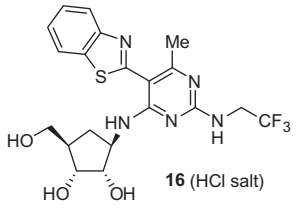
Compd #	R	EC_{50} (μM)	MTS/GAPDH CC_{50} (μM)	AUC[a] (μM.h)	Liver[b] C_{6h} (ng.g)
32	H[c]	0.02	18/14	0.08	<100
41	H[d]	0.2	>25/>25	0.4	250
42	H	0.13	25/4	4.7	–
43		0.05	>25/>25	2.7	75
44		0.1	>25/12	6.2	515
45		0.31	>25/>25	–	–
46		0.16	14/13	19.6	3320
47		0.09	13/12	5	1245
48		0.06	10/10	2.3	510
49		0.05	8/8	3.2	405
50		0.25	>25/>25	0.5	150
51	NHR = NMe_2	0.14	16/18	11[e]	1030
52	NHR = NMe_2[f]	13	>25/>25	–	–
53		0.035	15/21	5.9	875
54		0.035	18/18	2.4	400
55		0.020	7/8	0.9	130
56		0.04	19/12	0.3	63
57		0.9	>25/>25	–	–
58		0.26	>25/>25	–	–
59		0.04	25/25	0.2	370
16		0.03	17/25	7[e]	8415[g]
60[h]		0.8	>25/>25	–	–
61[i]		0.7	>25/>25	12.8	12765
62		0.14	>25/>25	13	6570
63		0.1	19/21	–	–
64		0.03	9/9	5.3	1075
65		0.03	4/3	2.1	2230
66		0.28	>25/>25	1.6	970
67		0.33	7/7	–	–
68		0.77	13/15	–	–
69		4.5	>25/>25	–	–
70		0.03	7/9	2.2	430

Table 2 (*continued*)

Compd #	R	EC_{50} (μM)	MTS/GAPDH CC_{50} (μM)	AUC[a] (μM.h)	Liver[b] C_{6h} (ng.g)
71		0.006	5/6	0.5	180
72		0.015	4/6	0.2	75
73		0.03	21/23	0.5	150
74		0.03	18/13	3.4	125
75		0.015	11/5	0.02	10
76		0.03	9/7	0.1	100

[a] $AUC_{0-6\ h}$, po (10 mpk), vehicle—0.4% mc.
[b] Liver conc at 6 h.
[c] Pyrimidine C-4 = Cl.
[d] Pyrimidine C-4 = H.
[e] AUC_{0-24h}.
[f] Pyrimidine C-4 = Et.
[g] Liver conc at 4 h.
[h] Enantiomer of **16**.
[i] Pyrimidine C-4 = cyclopropyl.



16 (HCl salt)

EC_{50} = 0.03 μM
MTS/GAPDH CC_{50} = 17/25 μM
DNA CC_{50} = 19 μM
Selectivity index (CC_{50}/EC_{50}) >550
Pharmacokinetic data
Rat: IV (2 mpk, 40%HPBCD); PO (10 mpk, 0.4% MC)
AUC_{0-24h} = 7 μM.h; F = 82%
Liver $Conc_{4h}$ (PO) = 8415 ng/g
Monkey: IV (1 mpk, 40% HPBCD); PO (3 mpk, 0.4% HPMC)
AUC_{0-24h} = 0.3 μM.h; F = 8%
Dog: IV (1 mpk, 40% HPBCD); PO (3 mpk, 0.4% HPMC)
AUC_{0-24h} = 7.8 μM.h; F = 35%

Figure 2. Profile of lead compound **16**.

on the pyrimidine ring. Hence we decided to remove or replace the 4-chloro functionality. Targets shown in Table 2 are the results of efforts directed toward both C-4, and more extensively, C-2 modifications. These compounds were prepared using routes shown in Scheme 3 or Scheme 4. After initial evaluation in the replicon assay, most of the compounds were subjected to rat in vivo studies. Inhibitors were dosed orally (10 mpk, $n = 2$ rats for each compound, formulation vehicle—0.4% mc) and plasma samples were collected at various timepoints till 6 h post-dose. Rat plasma exposure is reported as $AUC_{0-6\ h}$. The animals were sacrificed at 6 h; liver was harvested and processed to measure the compound concentration (liver C_{6h}). The results are depicted in Table 2.

Removal of the 4-chloro moiety of **32** provided inhibitor **41** (prepared via hydrogenation), which displayed a 10-fold loss in replicon potency, albeit with some improvement in rat plasma exposure. Replacement of the 4-chloro residue of **32** with a methyl group (**42**) resulted in some loss in potency. Interestingly, there was a significant increase in rat AUC for **42**. Hence, introduction of different functionalities on the pyrimidine 2-amino moiety was then studied extensively using the 4-methyl substituted target **42**. Installation of a series of alkyl residues on the 2-amino moiety was investigated first. Compared to **42**, the C-2 *N*-methyl derivative **43** displayed improved potency, good selectivity and rat plasma exposure. However, the target organ concentration was poor for **43**. The series of alkyl substituents studied (**44**–**50**, straight chain, branched, small cyclics) were equipotent or less potent than **43**. The rat pharmacokinetic profiles for the C-2 alkyl amino compounds were essentially similar, with the α-branched ones, **46** and **47**, exhibiting enhanced AUC and liver concentration. Introduction of an *N*,*N*-dimethylamino residue at C-2 position (**51**) resulted in potency loss, albeit with significantly improved rat AUC. The drastic loss of potency observed for inhibitor **52**, an analog of **51**, with a C-4 ethyl group demonstrated the SAR limitation for this position; only a methyl group was tolerated at the C-4 pyrimidine position.

To expand the scope of the C-2 amino alkyl substituent, we introduced heteroatoms and additional functionality on the alkyl chain. Inhibitors with ether-containing side chains (**53**–**55**) were very potent, with **53** showing good rat exposure and target organ concentration. Inhibitors with amino-derived functionality on the alkyl chain displayed mixed results; while the carbamoyl (**56**) and morpholino (**59**) containing targets showed very good potency, the urea (**57**) and sulfonamido (**58**) targets were less potent. Unfortunately, the potent compounds in this series (**56** and **59**) did not show appreciable rat plasma exposure. Introduction of a trifluoroethyl amino moiety at the C-2 position had a profound impact on the inhibitor profile. Thus, compound **16** exhibited very good replicon potency and selectivity. Moreover, **16** displayed excellent rat oral pharmacokinetic profile (AUC = 7 μM h) and target organ exposure (liver C_{4h} = 8415 ng/g). Several modifications were then carried out around compound **16**. The corresponding enantiomer, **60** (prepared from commercial carbasugar **5-***ent*—structure not shown) resulted in substantial erosion of potency. Significant loss in potency for **61**, with a C-4 cyclopropyl group, (prepared using cyclopropylboronic acid employing Suzuki conditions—see Scheme 3) once again confirmed the requirement of only a small methyl group at the C-4 position. Interestingly, compound **61** displayed some of the best rat in vivo profiles seen for this class of compounds. Introduction of an *(S)* or *(R)*-methyl group on the trifluoroethyl side chain, **62** or **63** respectively, resulted in a few fold loss in potency, while retaining the PK characteristics (for

62). Increasing the chain length between the C-2 amino moiety and the terminal trifluoromethyl group (compounds **64** and **65**) provided equipotent analogs, albeit with progressively diminishing selectivity and *in vivo* profile. Installation of aryl or heteroaryl group on the C-2 amino moiety was investigated next (**66**–**69**), which resulted in loss of replicon potency. However, an aryl or heteroaryl residue with a methylene spacer (**70**–**76**) on the C-2 amino moiety proved to be highly potent. For example, inhibitor **71** displayed excellent potency with an EC_{50} = 0.006 μM. Unfortunately, all compounds containing this substitution pattern (**70**–**76**) demonstrated poor oral AUC and/or liver concentration.

Having extensively explored the requirement for appropriate functionality on the C-2 amino moiety, and based on the potency, selectivity, rat oral and target organ exposure, we decided to advance inhibitor **16** for further evaluations in higher species. The full profile of **16** is shown in Figure 2. Thus, inhibitor **16** displayed very good potency and a high selectivity index. In rat in vivo studies, **16** exhibited high oral exposures, both in plasma and more importantly, the liver, which is the primary reservoir of HCV. Target **16** also demonstrated excellent rat oral bioavailability. While monkey plasma exposure was low, in dogs **16** exhibited good plasma concentration and oral bioavailability. Inhibitor **16** had no issues with CYP inhibition (3A4, 2D6, 2C9 >20 μM), and was clean in an in-house kinase panel counterscreen (22 kinases, IC_{50} >30 μM).

Our studies directed towards modifying the previously described carbanucleoside-like structure **1** resulted in benzothiazole moiety as an appropriate 5-substituent on the pyrimidine ring with improved HCV replicon potency. However, the parent C-2 amino analog **32** displayed poor rat plasma exposure. Replacement of the potentially reactive pyrimidine C-4 chloro residue with a methyl group provided enhanced rodent plasma exposure (analog **42**). Modulation of replicon potency and rat pharmacokinetic profile was carried out via introduction of a mono-substituent on the C-2 amino functionality. Different synthetic routes were employed to access the target compounds. While the initial Stille conditions proved effective in installing the 5-benzothiazole moiety, significant chemistry optimization towards a practical route resulted in a direct C–H arylation protocol on a fully substituted pyrimidine core, that was equally efficient and devoid of environmentally unfriendly tin reagent. Through extensive screening of various groups on the C-2 amino residue, inhibitor **16** was identified with the best overall profile (potency, selectivity, rat oral and target organ exposure). Inhibitor **16** was studied in higher species, where it displayed good plasma exposure and oral bioavailability in dogs. Thus, our lead optimization efforts to discover HCV replicase inhibitors from the novel carbanucleoside-like pharmacophore resulted in inhibitor **16** with desirable characteristics that warrant further investigations.

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